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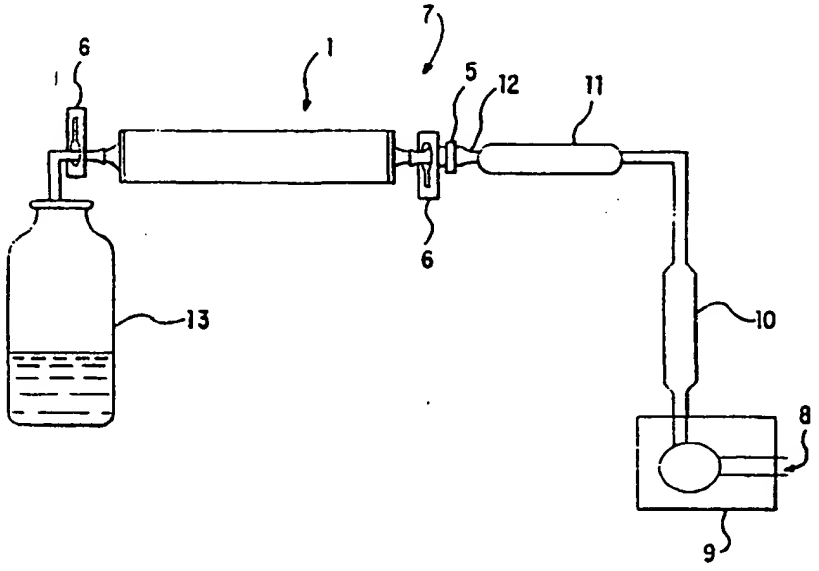
(54) Title: SYSTEM FOR PACKAGING AND DELIVERING OF A STERILE POWDER MEDIUM



(57) Abstract

A method and apparatus are disclosed for improved transfer and delivery of biological media used in tissue cell cultures. The media are reduced to powdered form, and then placed inside a cartridge or bag (1). The media are then sterilized within th bag (1) by the use of gamma irradiation. The cartridge or bag (1) is shipped to an end user, who reconstitutes the powder into solution. Sterilized water is pumped through the cartridge or bag (1), and solution exits from an outlet in the cartridge or bag (1) to a sterilized vessel (13). The solution can then be added to a tissue culture. The method is advantageous in that it does not require the solution to be filtered to be sterile, thus eliminating product losses during the filtering process. The method is also advantageous in that there is no direct handling of the powder after sterilization, thus greatly reducing the chance that the solution will be contaminated.

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System for Packaging and Delivering of a Sterile Powder Medium

Background of the Invention

The invention relates to techniques for the sterile delivery of products for biological uses, and specifically to an apparatus and method for providing sterile delivery of biological products without the need for passing the medium through a filter or sterilizing membrane filter.

In the generation of large-scale cell growth for the production of vaccines and biologicals, difficulties are encountered in attempting to prevent or eliminate contamination of a culture. The process of production will require the introduction of reagents, such as cell culture media, salts, sera, antibiotics, and proteins to stimulate the desired growth. These reagents must be prepared, and must remain, sterile so that they do not contaminate the culture when introduced into a culture vessel.

The methodology currently employed to prepare certain of these reagents involves the use powdered ingredients. Typically, these powdered reagents are not sterile when received by the end user, who converts these powdered ingredients into a solution using purified water. Since the solution is not sterile, as the powdered ingredients were not, the solution is then passed through a sterilizing membrane filter and transferred aseptically to a sterile container or culturing vessel.

The disadvantage of the above method is that such handling greatly increases the chances of biological contamination and loss or alteration of the product, contamination due to environmental or human exposures, loss due to transfer, and alteration due to removal of certain components during membrane sterilization.

Summary of the Invention

The drawbacks of the above system and apparatus are overcome by the method and apparatus of the invention.

In the present invention, the powder medium is stored in a cartridge or bag, which is then subject to gamma irradiation for sterilization. This results in delivering a powdered product to the end user in a sterile state. The cartridge or bag is designed so that the solution can be generated within the unit, eliminating potential opportunities for contamination. Since this invention eliminates the need for post-mixing sterilization, it reduces the potential for loss of product or components, thereby increasing batch-to-batch consistency.

Brief Description of the Drawings

Fig. 1 is a view of a powder delivery cartridge of the present invention.

Fig. 2 is a view of the reconstituting apparatus for the powder delivery cartridge of the present invention.

Fig. 3 is a view of a powder delivery bag of the present invention.

Fig. 4 is a view of the reconstituting apparatus for the powder delivery bag of the present invention.

Detailed Description

The present invention is directed to a method and apparatus for sterile delivery of cell culture products in solution. To facilitate the distribution and transport of biological products used in cell cultures, it is desirable when and

where possible to reduce the products to a stable powder form. At the point of use of the products, the powder is combined with sterile purified water to generate a liquid solution, which then may be transferred to the cell culture vessel or vessels.

In the system and apparatus of the present invention, powdered products are sealed in a container at the point of manufacture. The container is made of a material that is non-cytotoxic, impermeable to gas exchange, and sterilizable by gamma irradiation. Fig. 1 shows the apparatus used in a first embodiment of the present invention, where a powdered medium is contained within a cartridge. Cartridge 1 comprises a hollow cartridge barrel 2 (which may be, but is not limited to, a suitable IV blood filter cartridge), and has end caps 3, tubing 4, tubing connectors 5, and tubing clamps 6 connected at each end.

The procedure for assembly and filling of the cartridge 1 involves first connecting tubing connectors 5 to tubing 4, by coating tubing connectors 5 with solvent and inserting them into tubing 4. Tubing clamps 6 are then clamped onto both pieces of tubing 4. Next, tubing 4 is connected to end caps 3 by first applying solvent to end caps 3 and then inserting end cap 3 end into tubing 4 end. One end cap 3 is then attached to barrel 2 by coating the outside edge of the end cap 3 with solvent and connecting it to barrel 2 end. The cartridge 1 is then filled from the other end of barrel 2 with the appropriate amount of powdered medium. Powder should not be present on the inside edge of barrel 2. Finally, the other end cap 3 is attached to the open end of barrel 2, using the procedure outlined above, and the cartridge 1 is labelled to indicate the type and quantity of powdered medium therein.

The cartridge is then stored with a desiccant, at a temperature between 2-^{oo} C. The contents of the cartridge are next sterilized using gamma irradiation, generally between 0.5 and 3.0 megaRad. Finally, the cartridge is shipped, with a desiccant and at a temperature between 2-8° C, to the end user. The

configuration for a suggested apparatus for reconstitution by an end user of medium stored in a cartridge is illustrated in Fig. 2.

Reconstitution of the powdered medium is accomplished by connecting cartridge 1 to a reconstituting apparatus 7. Reconstituting apparatus 7 contains an inlet tube 8 which is connected to a source (not shown) of water, preferably WFI-grade water. Water is pumped from its source by a peristaltic pump 9, of any known type for accurate delivery of liquids. The outlet of peristaltic pump 9 is connected to a filter unit 10, preferably containing a sterile 0.2 μm filter.

Connected in series with filter unit 10 is a sodium bicarbonate cartridge 11, which has at one end tubing 12 which may be connected to the tubing connector 5 on cartridge 1. Sodium bicarbonate is necessary in the reconstitution process to act as a buffer for the powdered medium, but must be packaged separately due to potential problems of carbon dioxide generation. Although sodium bicarbonate is shown in Fig. 2 as added to the water through cartridge 11, it could, alternatively, be added to the water upstream of the peristaltic pump 9 at the water source, thus eliminating the need for sodium bicarbonate cartridge 11. Generally, sodium bicarbonate cartridge 11 should be gamma irradiated for sterilization.

In operation, the cartridge 1 is connected to tubing 12 on reconstituting apparatus 7 by means of tubing connector 5. Previously, sodium bicarbonate cartridge (if necessary) and filter 10 have been connected to peristaltic pump 9 to complete reconstituting apparatus 7. Clamp 6 on cartridge 1 adjacent tubing 12 is then unclamped. The unconnected tubing connector 5 on cartridge 1 is then aseptically joined to a sterilized receiving vessel 13. Next, clamp 6 on cartridge 1 adjacent sterilized receiving vessel 13 is unclamped. Peristaltic pump 9 is then activated. Liquid flows from its source, through peristaltic pump 9, filter unit 10, sodium bicarbonate cartridge 11, powder cartridge 1 and (as solution) into sterilized receiving vessel 13. Solution is therefore generated and placed into

vessel 13 without need for handling or filtering of the solution itself. The solution is sterile due to pre-cartridge filtering of the water and the previous gamma irradiation of the powder medium and sodium bicarbonate. Peristaltic pump 9 is run until the volume of solution generated in vessel 13 is of a desired quantity. Solution in vessel 13 may thereafter be transferred to specific cell culture devices.

Fig. 3 shows a second embodiment of the present invention, utilizing a powder delivery bag 14. Powder delivery bag 14, of appropriate manufacture so that it is compatible with cell culture usage, generally contains three ports: septum port 15, filling port 16, and dispensing port 17. Filling port 16 and dispensing port 17 consist of flexible tubing (as were the inlets and outlets to cartridge 1) to which are attached tubing clamps 18. During filling, the tubing clamps 18 are unclamped, and powder is dispensed into bag 14 through filling port 16. After filling is completed, tubing clamps 18 are clamped to both filling port 16 and dispensing port 17. The bag is then stored with a desiccant, at a temperature between 2-8° C. The contents of the bag are then sterilized using gamma irradiation, generally between 0.5 and 3.0 megaRad. Finally, the bag is shipped, with a desiccant and at a temperature between 2-8° C, to the end user. The end user reconstitutes the powder using the apparatus shown in Fig. 4.

The apparatus for reconstitution in powder bag 14 is similar to that used to reconstitute powder in powder cartridge 1. To reconstitute the powder, tubing connector 5 is connected between tubing 12 and filling port 16. Dispensing port 17 is connected to sterilized receiving vessel 13. Clamps 18 are then unclamped, and peristaltic pump 9 is activated. Liquid flows through pump 9, filter 10, sodium bicarbonate cartridge 11 (if necessary), bag 14, and (as solution) into vessel 13. Accordingly, as in cartridge 1, solution is dispensed into sterile receiving vessel 13 without the need to handle the powder and without the need to filter the solution. Bag 14 may be used for storage of the material for a prescribed period of time.

While the invention has been described with reference to specific embodiments, it will be apparent to those skilled in the art that many alternatives, modifications, and variations may be made. Accordingly, it is intended to embrace all such alternatives or modifications that may fall within the spirit and scope of the appended claims.

WHAT IS CLAIMED IS:

1. A method for delivering sterile biological media or cell culture reagents comprising the steps of:

filling a device with a powdered biological product;

sealing said powdered biological product in said device;

irradiating said device and said powdered biological product with gamma radiation;

connecting a source of sterile liquid to said device;

delivering said sterile liquid so as to continuously flow through said device;

collecting a resulting solution from said device in a sterile container; and

transferring a portion of said resulting solution from said sterile container into a receptacle containing a cell culture.

2. The method of claim 1, wherein:

said device is a cartridge.

3. The method of claim 1, wherein:

said device is a bag.

4. The method of claim 1, wherein:

said device and said powder are irradiated at a level between 0.5 and 3.0 megaRad.

5. The method of claim 1, wherein:

said device has two tubular conduits connected therewith;

said sterile liquid flows into one of said tubular conduits; and

said resulting solution flows out of the other of said tubular conduits.

6. The method of claim 1, wherein:

said tubular conduits are sealed by clamps between the step of filling the device and the step of connecting the source of sterile liquid to said device.

7. The method of claim 1, wherein:
said sterile liquid is sterilized as it flows to said device.

8. The method of claim 7, wherein:
said sterile liquid is sterilized using a filter through which the liquid flows as it moves towards said device.

9. A method for packaging a sterile powder of biological products comprising the steps of:
filling a rigid cartridge with a powder of biological products;
sealing the rigid cartridge;
subjecting the rigid cartridge and the powder to gamma irradiation.

10. The method of claim 9, wherein:
said device is filled with powder through a tubular conduit, which is sealed after filling by a clamp.

11. The method of claim 9, wherein:
said device and said powder are irradiated at a level between 0.5 and 3.0 megaRad.

12. An apparatus for reconstituting a powdered biological medium comprising:
a source of a reconstituting liquid;
a flow line through which said reconstituting liquid flows;
a sterilizer in said flow line which sterilizes said liquid as it flows through said flow line;
a buffering device in said flow line containing a buffering medium which is added to said liquid as it flows through said flow line; and

a connecting member connected to said flow line downstream of said sterilizer and said buffering device, said connecting member arranged to be connected to a device containing sterilized powdered biological medium.

13. The apparatus of claim 12, further comprising:

a device containing said sterilized powdered biological medium, said device being connected to said connecting member.

14. The apparatus of claim 13, wherein:

said device has two conduits, one of said conduits connected to said connecting member and the other of said conduits connected to a sterilized vessel.

15. The apparatus of claim 13, wherein:

said sterilized powdered biological medium has been sterilized within the device by gamma irradiation.

16. The apparatus of claim 12, wherein:

said sterilizer is a filter.

17. The apparatus of claim 14, wherein:

said other of said conduits contains no sterilizing means.

18. An apparatus for transporting and delivering biological products comprising:

a rigid cartridge constructed of a gamma radiation permeable material;

at least two conduits leading to the interior of said device; and

a powdered biological medium contained within said device; wherein

said at least two conduits are sealed after introduction of said powdered biological medium into said device, and said powdered biological medium is subjected to gamma irradiation after said at least two conduits are sealed.

19. The method of claim 1, further comprising the step of:
buffering said sterile liquid before it is delivered into said device.

20. The method of claim 19, wherein:
the step of buffering said sterile liquid comprises the steps of:
connecting a second device containing a sterilized, powdered buffer material to said source of sterile liquid;
delivering said sterile liquid into said second device.

21. The method of claim 20, wherein:
said sterilized, powdered buffer material is sterilized by gamma irradiation.

22. The method of claim 20, wherein:
said sterilized, powdered buffer material is sodium bicarbonate.

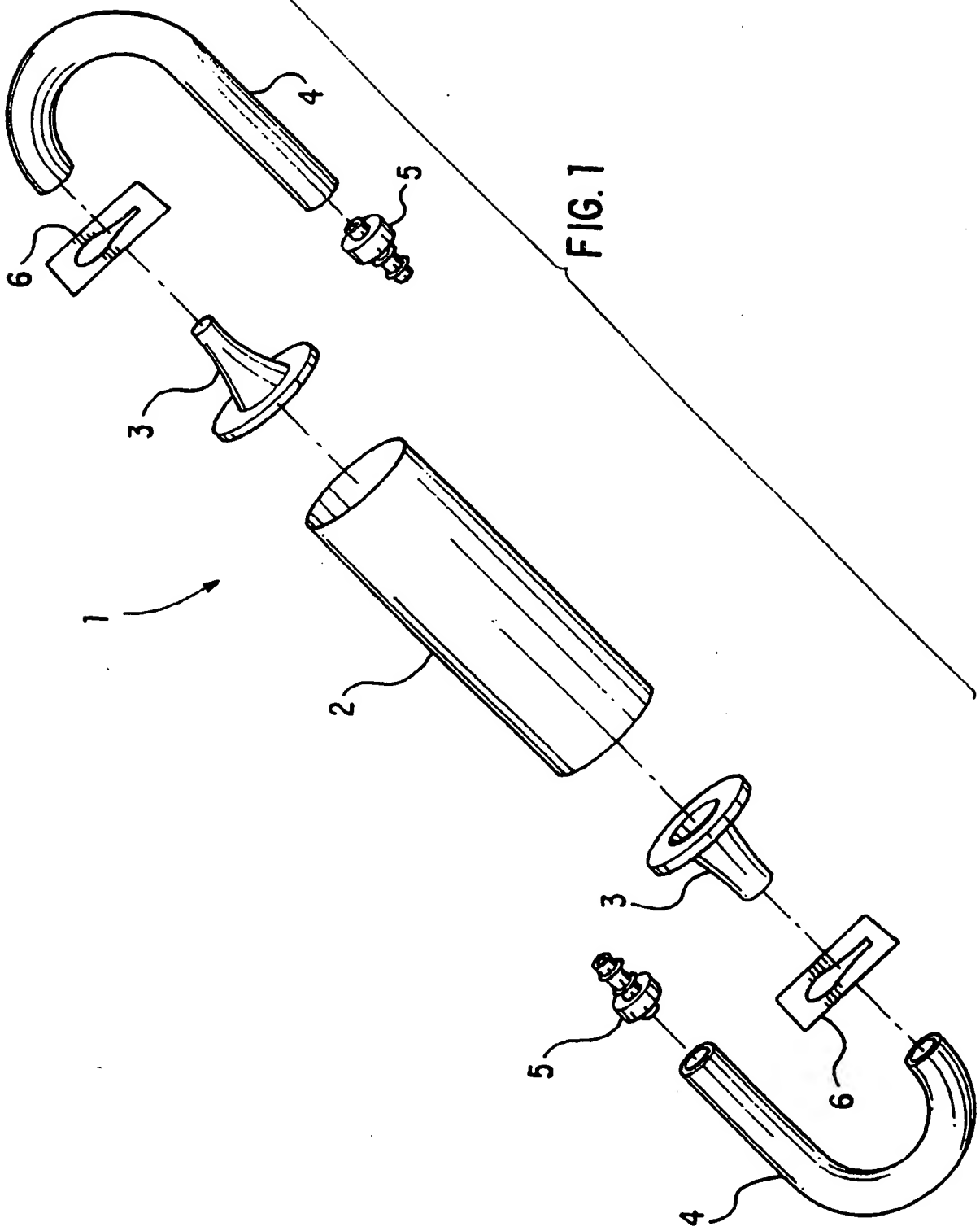

FIG. 1

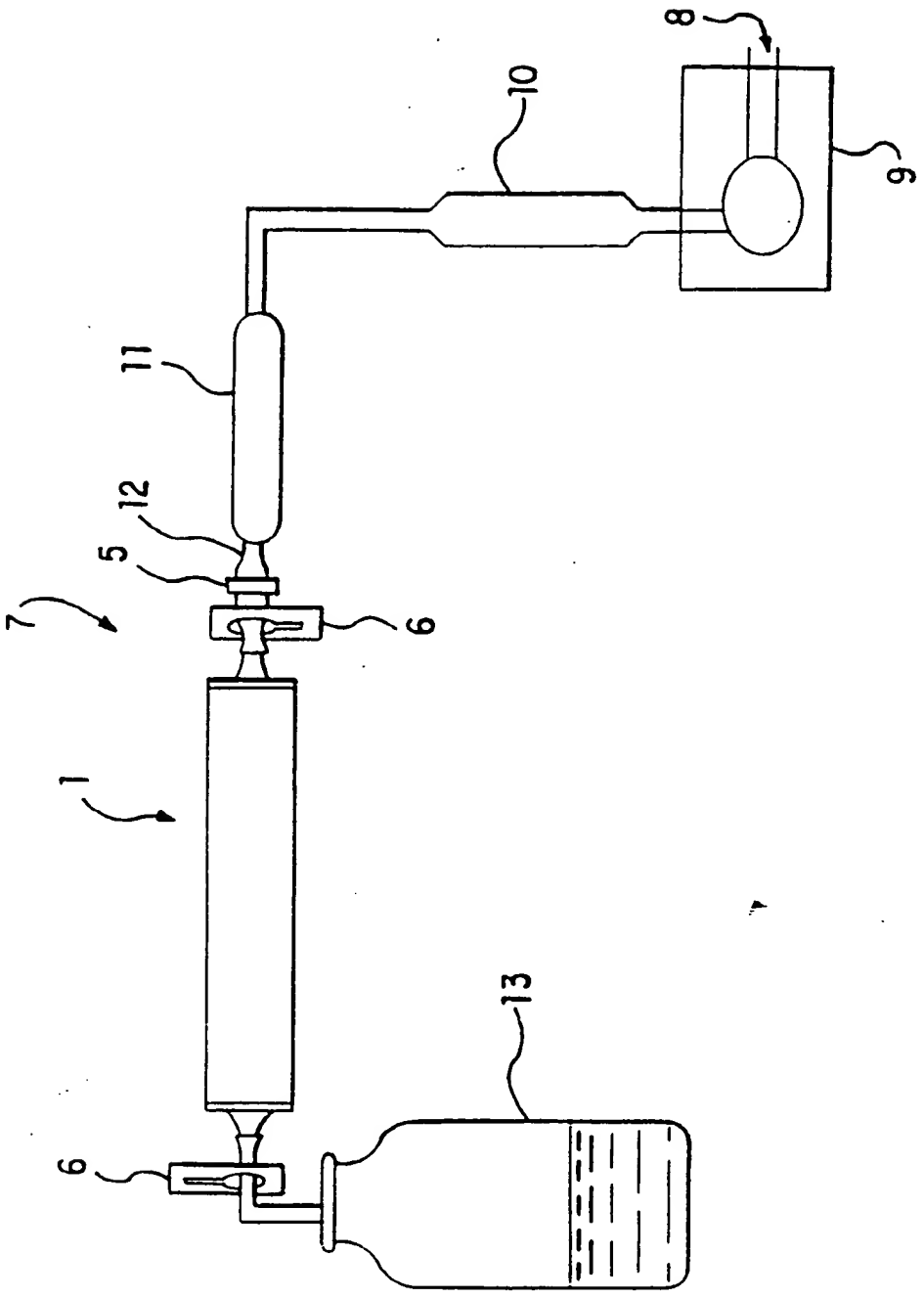

FIG. 2

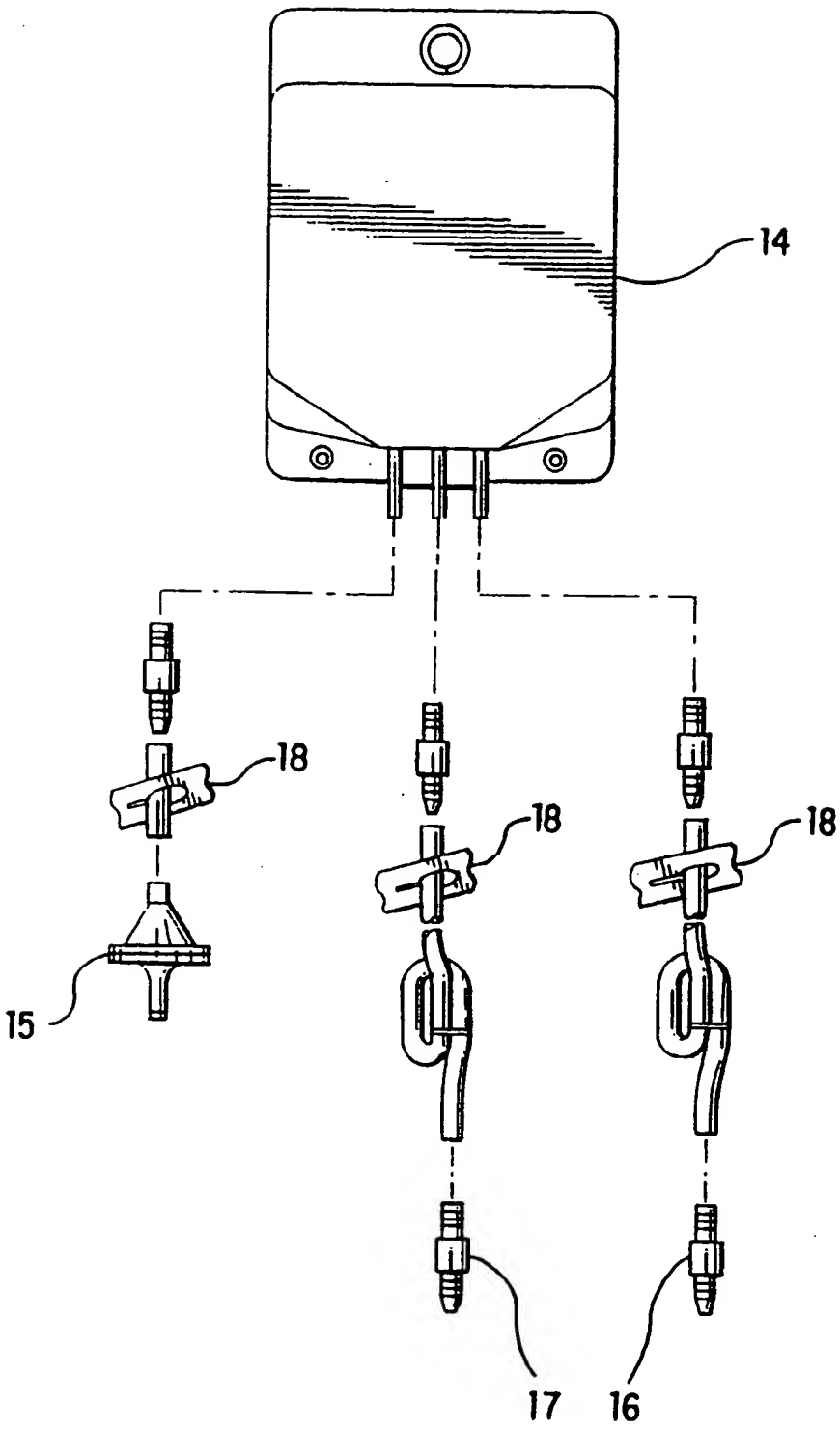

FIG. 3

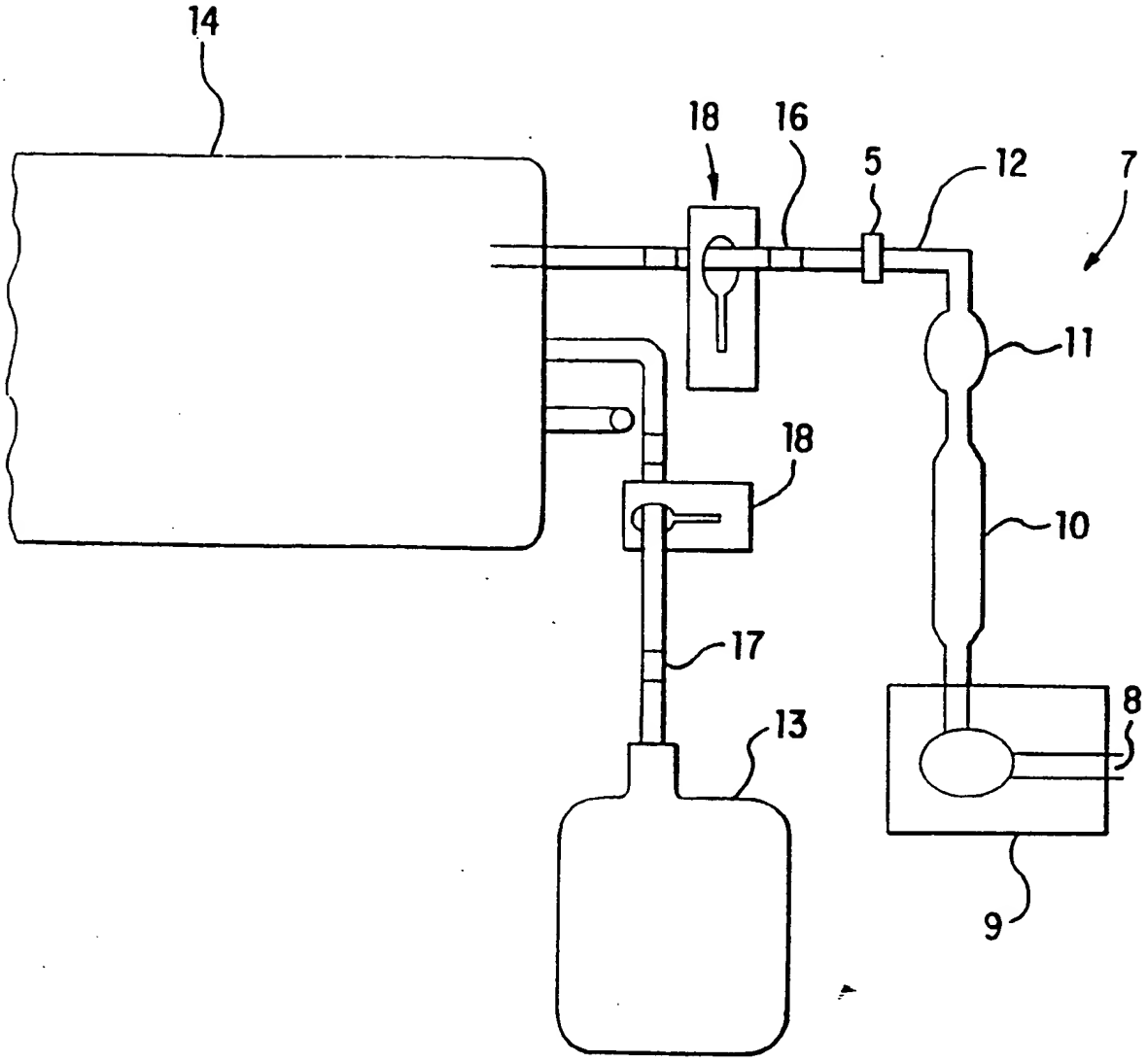

FIG. 4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/05175

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61L 2/00; B01J 19/00; C12M 1/22
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 422/22, 23, 40, 186.04, 255, 261, 292, 294, 905; 435/173, 297, 311, 810

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, search terms: powder, sterilize, gamma

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 4,282,863 (Beigler et al) 11 August 1981, see entire document.	1-8 and 19-22
Y	US, A, 4,784,495 (Jonsson et al) 15 November 1988, see entire document.	2, 9-22
Y	US, A, 5,116,575 (Badertscher et al) 26 May 1992, see entire document.	7-8 and 12-17

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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INTERNATIONAL SEARCH REPORT

International application No.
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A. CLASSIFICATION OF SUBJECT MATTER:
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